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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,697	09/27/2001	Tarlochan Singh Dhadialla	A9526	4412

80011 7590 12/09/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/965,697	DHADIALLA ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-12,15 and 21-47* is/are pending in the application.

4a) Of the above claim(s) *21-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,15 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/08, 10/15/08, 10/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 September 2008 has been entered.

Applicant's response, of 16 September 2008, is acknowledged and has been entered. Claims 6 and 14 have been canceled. Claims 1-4, 7-12, 15, and 21-47 are pending in the instant application. Claims 1, 2, 8, 9, 10, 15 and 47 have been amended and the amendment made of record.

Claims 21-46 stand withdrawn from consideration as being directed to a non-elected invention. Applicants traverse the withdrawal of the claims (Response of 16 September 2008, page 20, 1st paragraph). The reason for the traversal is that applicants have filed a request for continued examination under 37 CFR 1.114.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Applicants are referred to MPEP § 706.07(h) which describes RCE practice. The MPEP states:

> Applicants cannot file an RCE to obtain continued examination on the basis of claims that are independent and distinct from the claims previously claimed and examined as a matter of right (i.e., applicant cannot switch inventions). See 37 CFR 1.145. Any newly submitted claims that are directed to an invention that is independent and distinct from the invention previously claimed will be withdrawn from consideration and not entered. See subsection VI. below. An RCE is not the filing of a new application. Thus, the Office will not convert an RCE to a new application such as an application filed under 37 CFR 1.53(b) or a continued prosecution application (CPA) under 37 CFR 1.53(d)

Thus, the withdrawal of Claims 21-46 is proper and the claims stand withdrawn.

Claims 1-4, 7-12, 15 and 47 are under consideration.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 2 October 2008 and 23 October 2008 have been considered. The signed copies are attached.

The information disclosure statements filed 15 October 2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because References NPL 26 and 27 could not be found among the submitted documents. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Withdrawn Objections

The objection to the drawings and the "Brief description of the Drawings" in the specification is withdrawn in light of Applicants' amendment to the specification.

New/Maintained Rejections

35 U.S.C. § 101:

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4 and 12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as recited read on host cells still attached to an animal or a human, including any eukaryotic cell. There is no limitation wherein the host cells are isolated or in culture, therefore the claims read on transfected cells in a human, and thus are not patentable subject matter. This rejection could be overcome by adding a limitation wherein the host cells are isolated or in culture.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising the multiple gene regulation system, does not reasonably provide enablement for any generic host cell comprising the multiple gene regulation system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to a broad genus of host cells comprising a multiple gene regulation system. The specification contemplates three subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture, in gene therapy [paragraphs 0241, and 0243 of PGPUB US 2002/0110861, the PGPUB of the instant invention], and in multicellular, transgenic organisms [paragraphs 0256-0261].

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Since the instant specification asserts that the claimed host cells can be made and used in three contexts, two of which are not enabled for the reasons set forth below, the instant fact pattern corresponds to the second situation wherein the claims encompass a significant number of inoperative embodiments and thus should be rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claims.

The specification asserts that host cells can be made and used in three contexts.

1) The specification contemplates making and using isolated host cells in culture in such areas as proteomics, functional genomics, cell based high throughput assays, toxicology screening and large-scale protein production [paragraph 0241]. Such is enabled, since the specification and prior art provide

specific guidance on how to make and use host cells for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

2) The specification also asserts that the claimed gene regulation system can be expressed in transgenic animals and any technique known in the art may be used to introduce a transgene into animals to produce the founder lines of transgenic animals (paragraphs 0256-0261). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene regulation system is demonstrated to express an encoded peptide of interest. Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Thus, based on the art recognized unpredictability of producing transgenic animals which express the required gene regulation system and protein of interest, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals.

3) The specification also discloses that the gene regulation system can be used in vivo in gene therapy approaches (paragraphs 0241, and 0243). However, the specification does not teach any methods or working examples that indicate the system is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For

example, the specification does not teach what type of vector would introduce the claimed system into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed gene regulation system into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed gene regulatory system in the cell of an organism or be able to produce the protein of interest in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed gene regulation system and to introduce and express the claimed gene regulation system in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed gene regulation system in the cell of an organism to be able produce the encoded protein of interest, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this rejection could be overcome by amending the claims to recite, for example, "An isolated host cell…" because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture as described in context 1) above.

Claims 3 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a virus comprising:

(a) the multiple gene regulation system of claim 1 wherein the system comprises one or more polynucleotides encoding a receptor complex and a polynucleotide comprising: an exogenous or endogenous polynucleotide and a response element; and

(b) the multiple inducible gene regulation system of claim 9 wherein the system comprises a plurality of individually operable gene regulation systems wherein each individually operable gene regulation system comprises a polynucleotide comprising: an exogenous or endogenous gene; and a response element

does not reasonably provide enablement for:

(c) the multiple gene regulation system of claim 1 wherein the system comprises a ligand; and

(d) the multiple inducible gene regulation system of claim 9 wherein the system comprises a plurality of individually operable gene regulation systems wherein each individually operable gene regulation system comprises one or more receptor complexes and a ligand.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claims recite a virus comprising the multiple gene regulation system of claim 1 (Claim 3) and a virus comprising the multiple gene regulation system of claim 9 (Claim 11). Thus, the claims are drawn to viruses, including viral vectors, comprising not only nucleic acids, but ligands (compounds whose

chemical natures are not further specified) (Claims 3 and 11) and receptor complexes (proteins) (claim 11) as well.

The specification teaches "Several methods known in the art may be used to propagate a polynucleotide according to the invention. .... the expression vectors which can be used include, but are not limited to, the following vectors or their derivatives: human or animal viruses such as vaccinia virus or adenovirus; insect viruses such as baculovirus; yeast vectors; bacteriophage vectors (e.g., lambda), and plasmid and cosmid DNA vectors, to name but a few [paragraph 0062] Viral vectors, and particularly retroviral vectors, have been used in a wide variety of gene delivery applications in cells, as well as living animal subjects. Viral vectors that can be used include but are not limited to retrovirus, adeno-associated virus, pox, baculovirus, vaccinia, herpes simplex, Epstein-Barr, adenovirus, geminivirus, and caulimovirus vectors [paragraph 0064]. Thus, the specification envisions the use of viral vectors to introduce and propagate nucleic acids in a host cell and organism. However, the disclosure provides no guidance to the skilled practitioner as to how to construct and utilize a virus comprising a protein receptor complex and a ligand (of unspecified chemical nature), or how one is to introduce a vector comprising said protein receptor complex and ligand into a cell in such a way that these products would be propagated in and utilized by the cell. The working examples (Examples 1 and 2) teach transfection of cells with gene expression cassettes comprising nucleic acids and testing such cells for activity by exposing the cells to ligands such as ponasterone, and N-(2-ethyl-3-methoxybenzoyl)-N'-(3,5-dimethylbenzoyl)-N'-tert-butylhydraz-ine. The transfections were performed using lipofectamine. There are no examples, working or prophetic, teaching construction of viral vectors comprising nucleic acids and ligands or comprising receptor proteins, nucleic acids and ligands and utilizing such viral vectors in the methods disclosed in the specification.

The art does not compensate for the lack of direction in the specification. The art teaches that viral vector systems are utilitzed in gene therapy procedures, such as gene therapy approaches to cancer. These viruses

comprise nucleic acids that encode proteins for the viral coat and enzymes necessary for viral integration into host chromosome (See, for example, Kufe et al (ed) Cancer Medicine BC Decker Inc. 2003, pages 1-8, downloaded 12/3/08). However, there are no teachings in the art of viral vector systems comprising nucleic acids and ligands or comprising receptor proteins, nucleic acids and ligands as recited in the claims of the instant invention nor are there teachings of how to make or use such vectors.

Due to the large quantity of experimentation necessary to determine how to construct and utilize a viral vector comprising receptor proteins, nucleic acids and ligands, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that viruses comprise nucleic acids and viral coats, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The rejection of claims 1-4, 7-12, 15 and 47 as failing to comply with written description requirement is maintained for reasons of record and for reasons set forth below. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection (Response of 16 September 2008, page 21, 4th paragraph). The reason for the traversal are that independent claims 1, 9 and 47 have been amended to recite “a Group H nuclear receptor ligand binding domain and nuclear receptor ligand binding domain capable of forming a dimer with the Group H nuclear receptor ligand binding domain”; thus, the inventor s were in possession of the presently claimed invention.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The claims have been amended to recite receptor constructs comprising Group H nuclear receptor ligand binding domains and nuclear receptor ligand binding domains capable of forming dimers with the Group H nuclear receptor ligand binding domains The specification teaches Group H nuclear receptors consist of ecdysone receptor, ubiquitous receptor (UR), Orphan receptor 1 (OR-1), steroid hormone nuclear receptor 1 (NER-1), RXR interacting protein-15 (RIP-15), liver x receptor .beta. (LXR.beta.), steroid hormone receptor like protein (RLD-1), liver x receptor (LXR), liver x receptor .alpha. (LXR.alpha.), farnesoid x receptor (FXR), receptor interacting protein 14 (RIP-14), and farnesol receptor (HRR-1) [paragraph 0148]. The second nuclear receptor ligand binding domain may be a vertebrate retinoid X receptor ligand binding domain, an invertebrate retinoid X receptor ligand binding domain, an ultraspiracle protein ligand binding domain, and a chimeric ligand binding domain comprising two polypeptide fragments, wherein the first polypeptide fragment is from a vertebrate retinoid X receptor ligand binding domain, an invertebrate retinoid X receptor ligand binding domain, or an ultraspiracle protein ligand binding domain, and the second polypeptide fragment is from a different vertebrate retinoid X receptor ligand binding domain, invertebrate retinoid X receptor ligand binding domain, or ultraspiracle protein ligand binding domain [paragraph 0158]. Thus, the claims remain directed to a genus of multiple gene regulation systems comprising two or more individually operable gene regulation systems, wherein each individually system operates independently of any other ("is orthogonal").

However, the only systems described are ones comprising two independent systems (Examples 1 and 2), a Lepidopteran/Dipteran and a Lepidopteran/Homopteran ecdysone receptor system. The claims (1 and 9) are not limited to these systems or any systems with only two receptor expression cassettes, but are directed to multiple systems, comprising a plurality of individually operated gene regulation systems , i.e. having more than two, none

of which have been further described. The skilled artisan would not recognize that applicants were in possession of a genus of having multiple expression systems. Additionally, all the independent claims (1, 9 and 47), as amended, are still directed to a myriad of multiple gene regulation systems. Applicants have not identified any particular chemical structure that will provide the required specificity and uniqueness of binding between the ligand and the receptor for use in the claimed multiple orthogonal systems, but have identified the claimed systems solely by a function.

Applicants have described and outlined, at pages 40-43 [paragraphs 0204-0240], complex, art-recognized methods of searching for specific ligands and screening for novel cognate LBDs. The structures of ligands presented on page 40, as potential chemotypes ideal for use as ligands, comprise a natural ecdysteroid and a known diacylhydrazine. These compounds appear to be cross-interactive across insect species, which is contrary to that required by the claimed invention. Applicants teach that "an orthogonal ligand/receptor set does not exist within these two structural families". This is certainly not evidence of possession but indicates that to achieve the goal of a multiple, orthogonal gene regulation system, further experimentation is required (page 40, lines 8-15, paragraph 0205).

Thus, applicants have not disclosed any additional molecules as ligands nor have they identified any particular cognate LBDs. The methods outlined act as an invitation to design and discover which ligands-receptor pairs may work as the multiple gene regulatory systems of the instant invention.

Applicants' teachings are an invitation to experiment to design, identify and isolate appropriate receptor/ligand pairs which act orthogonally; the disclosure does not provide evidence that Applicants were in possession of such. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features.

An invitation for others to discover a representative number of species with known or disclosed correlation between function and structure of the polynucleotides or polypeptides of gene modulation systems or by a combination of such identifying characteristics does not reasonably provide one of skill in the art with sufficient information to reasonably visualize or predict which ligand/receptor pairs would be encompassed by the claims. Therefore, Applicants are not in possession of the claimed genus of "multiple inducible gene modulation system" and thus, the current claims do not comply with the requirement for written description under 35 USC 112, first paragraph.

Therefore, the Lepidopteran/Dipteran and Lepidopteran/Homopteran receptor schemes (of the Group H family of receptors) but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Conclusions:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao, /
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